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## (54) MEDICINE FOR PREVENTING/TREATING OSTEOPOROSIS

(57)Abstract:

PROBLEM TO BE SOLVED: To obtain a medicine for preventing/treating osteoporosis which enhances density and strength of bone without elevating the concentration of calcium in blood, by including an active type vitamin D and bisphosphonic acid as active ingredients.

SOLUTION: The medicine is obtained by including (A) one or more active type vitamin Ds selected from the group comprising 1  $\alpha$  -hydroxyvitamin D, 1  $\alpha$  -24-dihydroxyvitamin D, 1  $\alpha$  ,25-dihydroxyvitamin D, 1  $\alpha$  ,24,25-trihydroxyvitamin D, 24,24-difluoro-1  $\alpha$  ,25-dihydroxyvitamin D, and 26,26,26,27,27,27-hexafluoro-1  $\alpha$  ,25-dihydroxyvitamin D, and (B) one or more bisphosphonic acids selected from the group comprising alendronic acid, pamidronic acid, etidronic acid, and licedronic acid, as active ingredients. It is preferable to administrate active type vitamin Ds at, a rate of 0.1-20  $\mu$  g/d and bisphosphonic acids at a rate of 1-20  $\mu$  g/d.

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## DETAILED DESCRIPTION

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[Detailed Description of the Invention]

[0001]

[Field of the Invention] the active vitamins D by which this invention is used for prevention or the therapy of osteoporosis, and a BISUHOSUphone -- it is related with the drugs which contain acids as an active principle.

[0002]

[Description of the Prior Art] By the small intestine, active vitamins D, such as the 1alpha-hydroxyvitamin D<sub>3</sub> (1 alpha-OH-D<sub>3</sub>) and 1alpha, 24(R)-dihydroxy vitamin D<sub>3</sub>, 1alpha, and 25-dihydroxy vitamin D<sub>3</sub>, have an absorption acceleration operation of calcium, and to the bone, since it has an operation of adjusting osteoclasts and osteogenesis, they begin osteoporosis and are used as a remedy of the disease based on the various abnormalities in calcium metabolism. However, in respect of improvement in bone density and bone reinforcement, although the therapy agent which makes these active vitamins D an active principle was almost satisfactory, it had the fault that the side effect that a patient's calcium concentration in blood is raised arose.

[0003] on the other hand -- a BISUHOSUphone -- acids act specifically to the activated osteoclast, are considered to control osteoclasts by controlling the activity, begin osteoporosis and are used as a remedy of the disease based on the abnormalities in calcium metabolism.

[0004] however, a BISUHOSUphone -- although there was no side effect that a patient's calcium concentration in blood was raised unlike the therapy agent by which the therapy agent which makes only acids an active principle makes the above-mentioned active vitamins D an active principle, in respect of improvement in bone density and bone reinforcement, it was less than the therapy agent which makes the above-mentioned active vitamins D an active principle.

[0005]

[Problem(s) to be Solved by the Invention] Then, this invention persons aim at equivalent to these well-known therapy agents, or offering the drugs with which bone density and bone reinforcement can be raised more than it, and the calcium concentration in blood does not rise conventionally as a therapy agent of osteoporosis. Moreover, it aims at offering the drugs with which this invention persons can control lowering of bone density and bone reinforcement as preventive of osteoporosis, and the calcium concentration in blood does not rise.

[0006]

[Means for Solving the Problem] the active vitamins D conventionally used independently ,

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respectively when this invention persons inquired wholeheartedly about the effective component as a therapy agent of osteoporosis , and a BISUHOSUphone -- it make it possible to offer the osteoporosis therapy agent which maintained the balance of not raise improvement in bone density and bone reinforcement , and calcium concentration in blood by use acids together . furthermore -- according to research of this invention persons -- the above-mentioned active vitamins D and a BISUHOSUphone -- it makes it possible to offer a header and osteoporosis preventive for it not only to raising the lowered bone density and bone reinforcement, but having the effectiveness which controls lowering of bone density and bone reinforcement by using acids together.

[0007] namely, this invention -- active vitamins D and a BISUHOSUphone -- it is the osteoporosis preventive or the therapy agent which contains acids as an active principle.

[0008] Hereafter, this invention is explained to a detail.

[0009] As active vitamins D used by this invention, it is distinguished from the vitamin D where no physiological function is in itself, the vitamin D which has physiological functions, such as calcium and a bone metabolic regulation operation, is said, and an active vitamin D 2, active vitamins D 3, and those derivatives are included. As the example, it is 1alpha-hydroxyvitamin D, 1alpha, 24-dihydroxy vitamin D, 1alpha, 25-dihydroxy vitamin D, alpha [ 1 ] and 24, 25-trihydroxy vitamin D, 24, and 24-difluoro, for example. - It is 1alpha, 25-dihydroxy vitamin D, 26, 26, 26, 27 and 27, and 27-hexafluoro. - 1alpha, 25-dihydroxy vitamin D, etc. are mentioned. Especially, the 1alpha-hydroxyvitamin D 3 and 1alpha, 24(R)-dihydroxy vitamin D3, 1alpha, and 25-dihydroxy vitamin D3 are desirable. Moreover, as active vitamins D in this invention, you may be a kind of these, or two sorts or more of mixture, and the mixed rate is defined suitably.

[0010] As a dose of these active vitamins D, it is an amount effective in prevention or the therapy of osteoporosis, and since it is based on a patient's age, weight, the class of combination therapy, the frequency of a therapy, the class of effectiveness desired, or the prescribing [ for the patient ]-a medicine method, although there is no \*\*\*\*\* generally, when using as a therapy agent generally, it will usually be [ day ] 0.1micro g-20microg/day preferably 0.01micro g-100microg /. In the case of external preparations, it will usually be [ day ] 20microg/day from 1microg preferably 0.01micro g-100microg /. When using as preventive, it will usually be [ day ] 0.1micro g-0.5microg/day preferably 0.05micro g-5microg /.

[0011] the BISUHOSUphone used by this invention -- as acids, the Allen Delon acid, pamidronic acid, the etidronic acid, the Chill Delon acid, and risedronic acid can be illustrated. The Allen Delon acid is desirable especially. Moreover, these may be kinds, or may mix and use two or more sorts at a rate of arbitration.

[0012] a BISUHOSUphone -- as a dose of acids, it is an amount effective in prevention or the therapy of osteoporosis, and since it is based on a patient's age, weight, the class of

combination therapy, the frequency of a therapy, the class of effectiveness desired, or the prescribing [ for the patient ]-a medicine method, there is no \*\*\*\*\* generally, but when using as a therapy agent generally, 5mg - 400mg /will usually be [ day ] 10mg - 200mg/day preferably. In the case of external preparations, it will usually be [ day ] 20microg/day from 1microg preferably 0.01micro g-100microg /. When using as preventive, 1mg - 10mg /will usually be [ day ] 2 or 5mg - 5mg/day preferably.

[0013] the osteoporosis preventive or the therapy agent of this invention -- these active vitamins D and a BISUHOSUphone -- although it can mix and they can also be simultaneously prescribed for the patient that what is necessary is just what contains acids as an active principle, each can also be independently prescribed for the patient continuously.

[0014] Moreover, the count of administration per day of the osteoporosis preventive of this invention or a therapy agent can be performed in 1 time or 2 - 3 steps.

[0015] prescribing a medicine for the patient continuously [ before bone density etc. decreases greatly ] here, in using \*\* of this invention as preventive -- desirable -- especially -- a BISUHOSUphone -- acids -- it is desirable to prescribe a medicine for the patient in order of -> active vitamins D. It is desirable to perform simultaneous administration on the other hand, in using \*\* of this invention as a therapy agent.

[0016] Moreover, it not only can raise bone density and bone reinforcement, but the osteoporosis preventive or the therapy agent of this invention does not raise the calcium concentration in blood. When a well-known osteoporosis therapy agent, i.e., active vitamins D, is conventionally used as an active principle, this Although it has effectiveness in respect of improvement by bone density and bone reinforcement, it has the side effect that the calcium concentration in blood rises. on the other hand -- a BISUHOSUphone, when only acids are used as an active principle It compares, although there is no side effect that the calcium concentration in blood rises, and effectiveness was inadequate in respect of improvement in bone density and bone reinforcement. The osteoporosis preventive or the therapy agent of this invention active vitamins D and a BISUHOSUphone -- by using together two kinds with a different action mechanism of acids as an active principle It has the description at the point which made it possible to offer the drugs which maintained the balance which has the improvement effectiveness of a well-known osteoporosis therapy agent, an EQC or the bone density beyond it, and bone reinforcement conventionally, and does not have this side effect.

[0017] moreover, the active vitamins D of this invention, and a BISUHOSUphone -- acids can be pharmaceutical-preparation-ized by the well-known approach with those suitable excipients that see or are explained below. As an example of such a pharmaceutical form, oral agents, such as an elastic capsule, hard capsules, a tablet, and syrups, injections, or external preparations can be mentioned.

[0018] As this excipient, oily ester, such as vegetable oil (for example, corn oil, cotton seed oil, coconut oil, an almond oil, and peanut oil are mentioned) and a medium-chain-fatty-acid glyceride, straight mineral oil, vaseline, animal fat and oil, a cellulosic (for example, crystalline cellulose, hydroxypropylcellulose, the hydroxypropyl methylcellulose, and methyl cellulose are mentioned), a polyvinyl pyrrolidone, a dextrin, a lactose, a mannitol, a sorbitol, starch, etc. are mentioned. Moreover, additives, such as an antioxidant, a wetting agent, a viscosity stabilizer, and a coloring agent, can also be added if needed.

[0019] Specifically, oral agents, such as preventive of the osteoporosis of this invention or an elastic capsule of a therapy agent, a tablet, and a granule for dry syrup, can be manufactured by the approach indicated by JP,57-45415,B, JP,63-46728,B, JP,63-60007,B, and JP,61-87619,A.

[0020]

[Embodiment of the Invention] Hereafter, an example is given and explained about this invention.

[0021]

[An example 1 and the examples 1-3 of a comparison] The ovariectomy was given to the 40-weeks old rat (a Sprague-Dawley system, female). After it left it for 15 weeks and bone quantity decreased, they were administered orally for 12 weeks by independent or concomitant use as the Allen Delon acid disodium salt (dosage weight of 0.2mg/kg) and the 1alpha-hydroxyvitamin D 3 (it is written as "Onealfa" among the dosage g/kg weight of 0.02micro and drawing) were shown below. The rat was euthanized after administration termination, the centrum was isolated, and the bone density (BMD, g/cm<sup>2</sup>) of the 4-6th centra (L4-L6) was measured by dual-energy x-ray absorptiometry. The result was shown in drawing 1 .

The example 1 of a comparison; ovariectomy group (control)

the example 2 of a comparison -- example of; Allen Delon acid administration group  
comparison 3; Onealfa administration -- as for the example 1, as compared with the examples 1-3 of a comparison, improvement in bone density was checked from group example 1; Allen Delon acid + Onealfa concomitant use group drawing 1 .

[0022]

[Examples 2 and 3 and the examples 4-6 of a comparison] The ovariectomy was given to the 48-weeks old rat (a Sprague-Dawley system, female). The drugs for 20 or less weeks were prescribed for the patient as shown below from the next day before bone quantity and bone reinforcement carry out reduction initiation.

example of comparison 4; ovariectomy group (control); -- example of vehicle comparison 5; Allen Delon acid administration group; -- the Allen Delon acid disodium salt (dosage 0.5 mg/kg weight)

Example of comparison 6; Onealfa administration group; 1alpha-hydroxyvitamin D 3 (dosage 0.05 mug/kg weight)

example 2; -- Onealfa -> Allen Delon acid administration group; -- the 1alpha-hydroxyvitamin D 3 (dosage 0.05 mug/kg weight)

-> (Ten weeks) Allen Delon acid disodium salt (dosage 0.5 mg/kg weight) (ten weeks)

example 3; -- Allen Delon acid -> Onealfa administration group; -- the Allen Delon acid disodium salt (dosage 0.5 mg/kg weight)

(Ten weeks) -> 1alpha-hydroxyvitamin D 3 (dosage 0.05 mug/kg weight) (ten weeks)

the rat after administration termination is euthanized -- making -- lumbar vertebrae -- isolating -- dual-energy x-ray absorptiometry -- the bone density (BMD, g/cm<sup>2</sup>) of the 3rd lumbar vertebrae (L3) -- moreover, maximum load (N) was measured by the centrum compression test. The result was shown in drawing 2 and drawing 3 . Furthermore, the calcium concentration in a blood serum was shown in drawing 4 .

[0023] Examples 2 and 3 showed the reduction depressor effect of the bone density of equivalent lumbar vertebrae, and bone reinforcement (it measures by the maximum overload) as compared with the examples 4-6 of a comparison the passage clear from drawing 2 and drawing 3 . Moreover, when examples 2 and 3 were compared, bone density and bone reinforcement improved from the group which the direction of the group which prescribed the example 3, i.e., the Allen Delon acid, for the patient in early stages medicated with Onealfa in early stages.

[0024] Moreover, the passage clear from drawing 4 , compared with the examples 4-6 of a comparison, calcium concentration in a blood serum is pressed down low, and examples 2 and 3 became clear [ that there is no side effect ].

[0025]

[Effect of the Invention] The osteoporosis preventive or the therapy agent of this invention can raise bone density and bone reinforcement conventionally as a therapy agent of osteoporosis equivalent to these well-known therapy agents, or more than it. And it is the drugs with which the balance not going up was able to take the calcium concentration in blood, and they are the drugs which maintained the balance which can control lowering of bone density and bone reinforcement also as preventive of osteoporosis, and does not go up the calcium concentration in blood further.

## CLAIMS

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[Claim(s)]

[Claim 1] active vitamins D and a BISUHOSUphone -- the osteoporosis preventive which contains acids as an active principle, or a therapy agent.

[Claim 2] the osteoporosis preventive according to claim 1 whose active vitamins D are a kind or two sorts or more of active vitamins D chosen from the group which consists of

1alpha-hydroxyvitamin D, 1alpha, 24-dihydroxy vitamin D, 1alpha, 25-dihydroxy vitamin D, alpha [ 1 ] and 24, 25-trihydroxy vitamin D, 24, and 24-difluoro-1alpha, 25-dihydroxy vitamin D, 26, 26, 26, 27 and 27, and 27-hexafluoro-1alpha and 25-dihydroxy vitamin D, or a therapy agent.

[Claim 3] a BISUHOSUphone -- a kind chosen from the group which acids become from the Allen Delon acid, pamidronic acid, the etidronic acid, the Chill Delon acid, and risedronic acid, or two sorts or more of BISUHOSUphones -- the osteoporosis preventive according to claim 1 or 2 which is acids, or a therapy agent.

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